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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,696	12/03/2003	Chaitan Khosla	300622000508	8649

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,696	KHOSLA ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *15-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I, claims 1-14, in the reply filed on February 23, 2006 is acknowledged.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-14 are directed to a method of modifying any polyketide synthase (PKS) by substituting the acyltransferase (AT) domain in a module by another from different module from the same gene cluster or from a different gene cluster. The specification, however, only provides two representative species in which AT domains of DEBS are replaced with AT domains from the gene cluster encoding rapamycin (RAP) and *visa versa*. The DEBS and the RAP gene clusters were the only known gene clusters encoding the biosynthetic pathways for polyketides at the time of invention, see the paragraph bridging pages 8 and 9. Among the genes that are reported in the specification to be mapped or partially sequenced, there is no teaching of a structure of any nucleic acid encoding any PKS or any AT domain from any of them. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these DNAs by any identifying structural characteristics or properties other than the activities recited in claim 1, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to polyketide synthase of the DEBS and RAP gene clusters as a source of the PKS and the AT domain. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to a method of making any modified PKS from any biological source in which the AT domain is replaced by another from any biological source (claims 1-10 and 17-26). Claims 11-16 are directed to a vector and host cell comprising a nucleic acid encoding said modified PKS. Factors to be considered in determining

whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a method of modifying any PKS by substituting the acyltransferase (AT) domain by another AT domain from any other PKS. The specification provides guidance and examples in the form of an assay to make a nucleic acid encoding modified PKS by substituting the AT domain in DEBS and RAP with another AT domain from DEBS or RAP (examples 1-4). While molecular biological techniques and genetic manipulation to make the constructs claimed are known in the prior art and the skill of the artisan are well developed, knowledge regarding the gene clusters or gene encoding PKS's from any biological source source and their genomic organization as well as the acyltransferases specificity in each of the polyketide synthases and their substrate specificity is lacking. Thus, searching for a gene cluster encoding any PKS, let alone a nucleic acid encoding a modified PKS in which an AT domain is replaced by another AT domain from another PKS, is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a gene cluster, identify the different open reading frames, and identify the AT domains is enormous. Since routine experimentation in the art does not include screening vast numbers of genomic and cDNA libraries from various microorganisms where the expectation of obtaining the desired gene cluster is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the nucleic acid sequence of the gene clusters, the open reading frames, and the various segments coding for each domain in each open reading frame. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Katz *et al.* (Katz, WO 93/13663).

Katz teach a method for obtaining novel polyketides by introducing specific changes in the DNA encoding the biosynthetic pathway of a polyketide, the summary of invention on page 2, the DNA sequence for the *ery* gene cluster and the amino acid sequences of the three open reading frame encoded thereby, see Figure 2, and exemplify the changes in the *ery* gene cluster (also known as DEBS). Figure 1 describes the various enzymatic activities in each open reading frame. Also, they teach that the extender unit employed at each condensation is specified by the acyltransferase function determined by each module, see page 6, lines 26-29, and the production of polyketide in microorganisms producing polyketide such as *Saccharapolyspora erythrea*, *Streptomyces antibioticusl*, *S. hygroscopicus* and *S. venezuelae* among others, see page 4, last paragraph. The method taught by Katz encompasses transforming a polyketide producing microorganism with the modified nucleic acid and culturing the microorganism and harvesting the product polyketide. The instant claims are directed to a method for modifying the acyltransferase activity in a modular polyketide synthase by another acyltransferase activity, a modification described by Katz as type III changes using restriction enzymes, see page 7, lines 12-18; and examples 7, 11, 15, 19, and 24. Specifically, Katz teach the replacement of the acyltransferase in any module by another acyltransferase from the same gene cluster or different gene cluster such as that of *S. venezuelae* wold be expected to produce predictable change in the structure of polyketides, see page 35, line 17-36. Also, claim 16 of Katz is drawn to a method for directing the biosynthesis of specific polyketide by genetic manipulation, which includes the replacement of a nucleic acid encoding an acyltransferase activity by another nucleic acid encoding an acyltransferase activity with different specificity (1-3, 7, 8, 10, and 14). In addition, Katz teach that the method is applicable to any gene cluster including those encoding the biosynthetic pathway of rapamycin (produced by *S. hygroscopicus*), avermectin, FK-506, and tylosin (claims 4-7 and 11-13), see page 36, lines 10-20.

Claims 1-14 are rejected under 35 U.S.C. § 102(e) as being anticipated by U. S. P 5,824,513 ('513, IDS reference number 5).

The '513 patent appear to be identical to Katz (WO 93/13663). It teaches a method for obtaining novel polyketide by introducing specific changes in the DNA encoding the biosynthetic pathway of a polyketide, the summary of invention, the paragraph bridging columns 1 and 2, the DNA sequence for the *ery* gene cluster and the amino acid sequences of the three open reading frame encoded thereby, see Figure 2, and exemplify the changes in the *ery* gene cluster (also known as DEBS). Figure 1 describes the various enzymatic activities in each open reading frame. Also, it teaches that the extender unit employed at each condensation is specified by the acyltransferase function determined by each module, see column 4, lines 52-56, and the production of polyketide in microorganisms producing polyketide such as *Saccharapolyspora erythrea*, *Streptomyces antibioticusl*, *S. hygroscopicus* and *S. venezuelae* among others, see column 3, lines 30-50. The method taught in the 513 patent encompasses transforming a polyketide producing microorganism with the

modified nucleic acid and culturing the microorganism and harvesting the product polyketide. The instant claims are directed to a method for modifying the acyltransferase activity in a modular polyketide synthase by another acyltransferase activity, a modification described in the patent as type III changes, see column 4, lines 16-21. Specifically, the '513 teaches the replacement of the acyltransferase in any module by another acyltransferase from the same gene cluster or different gene cluster such as that of *S. venezuelae* would be expected to produce predictable structure change in the polyketide, see starting in column 23, line 31 through line 5 of column 24. Also, claim 1 in the '513 patent is drawn to a method for directing the biosynthesis of specific polyketide by genetic manipulation which includes the replacement of a nucleic acid encoding an acyltransferase activity by another nucleic acid encoding an acyltransferase activity with different specificity, see claim 1 (c)(vi). In addition, the '513 patent teaches that the method is applicable to any gene cluster including those encoding the biosynthetic pathway of rapamycin, avermectin, FK-506, and tylosin (claims 1-6), see column 23, line 47 through column 24, line 32. Finally, they teach the use of restriction enzymes to carry out the modification of the nucleic acid *in vivo* and the use (claims 7, 8 and 10-14), see examples, which describe the various methodology of substituting domains combinations of plasmids and restriction enzymes.

Claims 1-14 are rejected under 35 U.S.C. § 102(e) as being anticipated by U. S. P 6,200,813 ('813, IDS reference number 14).

The '813 patent matured from an application which is a continuation in part of the application that matured to the '513 patent. Claims 1-10 of the '813 patent are fully enabled in the '513 patent, see the above rejection. It teaches and claims a method for altering the substrate specificity of a polyketide synthase by replacing the nucleic acid encoding an acyltransferase domain in a polyketide synthase by another nucleic acid sequence encoding an acyltransferase domain from another, see the paragraph bridging columns 3 and 4, and claims 1-10 of the patent. Also, it teaches the entire *ery* gene cluster which encodes the DEBS polyketide synthase, its organization, and its nucleic acid sequence, see Figure 2 and column 13, lines 48 and 49, as well as several nucleic sequences of several acyltransferase domains from *Streptomyces venezuelae* and *Streptomyces caelestis* having the nucleic acid sequences of SEQ ID NO's: 1, 2, 29, and 30 encoding the acyltransferase domains of SEQ ID NO's: 31, 32, 33, and 34 from various organisms. Furthermore, it teaches that the extender unit employed at each condensation is specified by the acyltransferase function determined by each module, see the paragraph bridging columns 13 and 14, and the production of polyketide in microorganisms producing polyketide such as *Saccharapolyspora erythrea*, *Streptomyces antibioticusl*, *S. hygroscopicus* and *S. venezuelae* among others, see column 13, lines 14-25. The instant claims 1-8 and 10-14 are directed to same claimed invention of the '813 patent which are also enabled in the '513 patent, see claims 1-10 of the '813 patent and the teaching of the '513 patent summarized above. Examples 1-3 and 9-10 teach the cloning of the nucleic acid encoding an acyltransferase domain from *S. hygroscopicus* (LigAT2) and *S. venezuelae* (venAT),

and the use of LigAT2 and venAT to construct vectors in which the *ery* gene cluster acyltransferase of module 1 is replaced with LigAT2 and venAT in *E. coli*. Examples 4 and 11 teach the construction of a host cell wherein the host cell is a polyketide producing bacterial cell such as *Saccharomyces erythrea*. Examples 18-28 represent other example of modifying *ery* gene cluster with other acyltransferase domain from different organisms. Claim 18 of the '813 is directed to various vectors comprising specific AT domain such as LigAT2, venAT, and rapAT14 as well as various AT domain modification of the *ery* gene. Applicants should note, while none of examples 1-28 is found in the priority documents for the '813 patent, i. e., the '513 patent, the claims are fully enabled in the priority document except for acyltransferase domain with specific nucleic/amino acid sequence other than those of the *ery* gene cluster.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz *et al.* (Katz, WO 93/13663) in view of Jasin *et al.* [4,713,337, ('337)].

The teaching of Katz *et al.* is summarized above.

The '337 patent teaches the utilization of a temperature sensitive plasmid in homologous recombination *in vivo*, see Figure 1.

The Katz patent document provide one of ordinary skill in the art with motivation to substitute an At domain in the gene cluster of a polyketide synthase by another AT domain having different specificity for an extension unit as they teach the production of novel polyketides, see examples. It would have been obvious to one of ordinary skill in the art at the time of invention to obtain the *ery* gene cluster in a first plasmid, identify the various AT domains, and transform a host cell with said plasmid as taught by Katz *et al.* It would have been further obvious to the ordinary skill in the art to obtain restriction fragments encoding the AT domain from the same gene clusters or a different gene cluster flanked with an up and down stream sequences known from the entire gene cluster taught by Katz *et al.* and construct a temperature sensitive second plasmid for homologous recombination *in vivo* as taught in the '337 patent (claims 7-14). It should be noted that the ordinary skill in the art would have been motivated to use the temperature sensitive plasmid because it can be removed and prevent further recombination events, see the last paragraph of the abstract. Thus, the claimed

invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,391,594 ('594). Although the conflicting claims are not identical, they are not patentably distinct from one another. Claims 1-6 of the '594 patent are drawn to a method of preparing a nucleic acid encoding modified erythromycin PKS comprising replacing the natural AT domain that employ malonyl as a substrate with another AT domain from the rapamycin accepting methylmalonyl as a substrate. Claims 1-14 of the instant application are drawn to a method of modifying the At domain in any polyketide synthase by substituting an AT domain by another from a different polyketide synthase which essentially the same method of claim 1-6 of the '594 patent. The claims of the instant application are broader in scope than those of '594 as they are directed to the modification of any AT in any PKS gene cluster from any biological source using any AT domain from any PKS from any gene cluster having different substrate specificity.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1656